Remarks

Claims 1-39 are currently pending in the application. Claims 5, 6, 24, 26, 28-34, and 36-39 are withdrawn. Claims 1-4, 7-23, 25, 27, and 35 currently stand rejected. Claims 2 and 16 are cancelled. Claims 1, 3, 4, 7, 8, 21, 22-28, and 33-29 are amended. The rejections levied in the Office Action are addressed individually below.

1. **Rejections under 35 U.S.C. § 112, 2nd paragraph.** Claims 1-4, 7-21, 23, 25, 27, and 35 are rejected under 35 U.S.C. § 112, 2nd paragraph, as being "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Specifically, the Examiner states that in claim 1, "it is unclear what conditions are encompassed with the suitable conditions to effect ligation" and "it is unclear if the temperature, the time, the buffer conditions, reagent and others effect ligation." Applicant respectfully disagrees and submits that one of ordinary skill in the art would understand that various conditions (*e.g.*, temperature, time, reagents, solvent, *etc.*) could be used in the claimed method. Solely in order to expedite prosecution, Applicant has amended claims 1 and 8 to recite "reducing reaction conditions employing an excess of a reducing agent." Applicant respectfully requests that the rejection be removed.

The Examiner states that in claim 1, "it is unclear what is meant by two consecutive, non-adjacent amino acids bearing A-L^1-moieties." In order to lend greater clarity to claim 1, Applicant has removed this lanuguage from the claim. Applicant submits that the structures recited in claim 1 of the peptide acyl donor and peptide amine acceptor provide enough clarity as to the structure of the cysteine-containing polypeptide product. Applicant respectfully requests that the rejection be removed.

The Examiner states that in claim 1, "it is unclear what R^{X0} is since it seems to be referring back to the moiety $-C(=O)OR^{X0}$ also has the variable R^{X0}." Applicant respectfully disagrees and submits that the definition of R^{X0} is essentially any group that would allow the $-C(=O)OR^{X0}$ moiety to undergo ligation with the peptide amine acceptor. Solely in order to expeditite prosecution, Applicant has amended claim 1 to recite R^{X0} as being a "disulfide-substituted aryl moiety." Applicant respectfully requests that the rejection be removed.

The Examiner asserts that in claim 7, "it is unclear what KH-1, STN, (2,3)ST, Le^y, Le^x, N3, Tn, 2,6-Stn, Gb3, and TF stand for and what these encompass. . . they appear not to be commonly known in the art." Applicant respectfully disagrees. It would be obvious to one of ordinary skill in the art, having read the specification, that claim 7 recites a list of carbohydrate moieties (see, for example, page 25, paragraph [0059] of the application as filed). Furthermore, one of ordinary skill would be aware of the structures of these carbohydrate moieties, as they were known in the art at the time the present application was filed. As evidence of this, Applicant has provided herewith a copy of the following references. Applicant respectfully requests that the rejection be removed.

Exhibit A: Danishefsky, S.J.; Allen, J.A.; *Angew. Chem. Int. Ed.* **2000**, *39*, 836-863; see Figures 1 and 8 describing the structures of KH-1, STn, 2,6-ST, (2,3)ST, Le^y, N3, Tn, and TF.

Exhibit B: Wormald, M.R. *et al.*, *Biochemical and Biophysical Research Communications*, **1991**, *180*, 1214-1221; see Figure 1 describing the structure of Le^x.

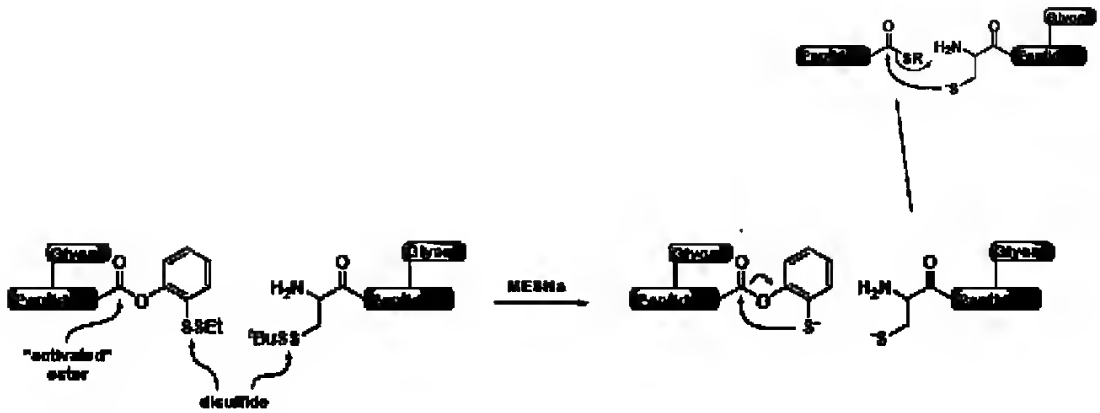
Exhibit C: Bosse, F. *et al.*, *J. Org. Chem.* **2002**, *67*, 6659-6670; see Figure 1 describing the structure of Gb3.

The Examiner asserts that in claim 17 "it is unclear what 'SS' is, since it is not defined in the claims." Applicant respectfully points out that "SS" refers to a disulfide bond "S-S". Support for this clarification is found throughout the specification wherein figures depicting "SS" are described as containing disulfide groups. See, for example, page 30, paragraph [0070]; page 35, paragraph [0086]; and page 44, paragraph [0111] of the application as filed. Applicant respectfully requests that the rejection be removed.

2. **Rejection under 35 U.S.C. § 112, 1st paragraph.** Claims 1-3, 8-23, 25, and 27 are rejected under 35 U.S.C. § 112, 1st paragraph, as failing to comply with the written description requirement. The Examiner finds that "the working examples describe glycan conjugated peptides being chemically ligated together," but asserts that "the specification does not describe any other A, A1, and A2 that are aliphatic, heteroaliphatic, aromatic, heteroaromatic, aryl, heteroaryl or a pharmaceutically useful group or entity." The Examiner concludes that "there is

not sufficient amount of examples provided to encompass the numerous characteristics of the whole genus claimed." Applicant respectfully disagrees.

The present invention claims methods of peptide ligation. As depicted in one embodiment, in Scheme 2 (see page 35, paragraph [0087] of the application as filed) the present invention provides a method of ligating a peptide with a C-terminal activated ester to another peptide with an N-terminal disulfide moiety:



It should be appreciated that Applicant's invention is in the provision of a peptide acyl donor comprising an activated ester (*i.e.*, the $-C(=O)OR^{X0}$ group of claim 1), a peptide amine acceptor comprising an $-SR^{S1}$ group, and the recognition that these two groups undergo ligation to provide peptides. This contribution, it is submitted, is not dependent upon any certain peptide sequence or any certain functional groups A, A1, or A2 on the peptides sequences. Therefore, Applicant contends that a requirement for Applicant to restrict the claims to certain A, A1, or A2 groups would represent an undue restriction of the scope of the claims. Instead, reference to compound or substituent classes, the meaning of which would be readily apparent to one of ordinary skill in the art, is appropriate. It is respectfully submitted that the teaching of the application is sufficient to enable a skilled practioner, using the accumulative knowledge in the field of protein synthesis, to put the invention into practice over the scope of the claims.

Applicant respectfully points out that claim scope is not limited to those embodiments actually disclosed in the specification. Indeed, broad claims may be supported without even a single disclosed embodiment (*In re Strahilevitz*, 668 F.2d 1229, 212 U.S.P.Q. 561 (C.C.P.A

1982). A specification may, within the meaning of 35 U.S.C. 112, first paragraph, contain a written description of a broadly claimed invention without describing all species that claim encompasses, and the embodiment need not necessarily have even been reduced to practice (*Spectra-Physics Inc. v. Coherent Inc.*, 827 F.2d 1524, 3 U.S.P.Q.2d 1737 (Fed. Cir. 1987); see also *Utter v. Hiraga*, 845 F.2d at 998, 6 U.S.P.Q.2d at 1714).

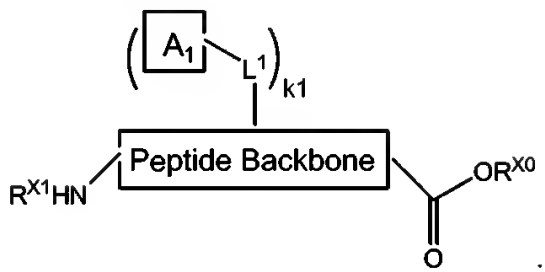
In response to the Examiner's assertion that the "specification does not describe any other A, A1, and A2 that are aliphatic, heteroaliphatic, aromatic, heteroaromatic, aryl, heteroaryl or a pharmaceutically useful group or entity," Applicant respectfully points out that a number of amino acid side-chain groups satisfy the definitions of aliphatic, heteroaliphatic, aromatic, or heteroaromatic. For example, a phenylalanine side chain group can be $-L^1$-A, wherein L^1 is methylene and A is aromatic; a serine or cysteine side chain group can be $-L^1$-A, wherein L^1 is methylene and A is heteroaliphatic; an arginine side chain group can be $-L^1$-A, wherein L^1 is propylene and A is heteroaliphatic; a valine side chain group can be $-L^1$-A, wherein L^1 is $-CHCH_3$ and A is aliphatic; and a histidine side chain group can be $-L^1$-A, wherein L^1 is methylene and A is heteroaliphatic. Moreover, Applicant has described numerous working examples utilizing peptide fragments containing different amino acids, different N-linked glycans, and O-linked glycans, all of which can be considered different $-L^1$-A groups. Also, one of ordinary skill in the art would be familiar with techniques for introducing other pharmaceutically useful groups or entities into the peptide as $-L^1$-A groups. Solely in order to expedite prosecution, Applicant has amended claims 1 and 8 to remove the phrase "pharmaceutically useful group or entity."

The Examiner appears to believe the instant claims are drawn to pharmaceutical activity of peptides. Instead, the claims are drawn to methods of preparing peptides. For example, the Examiner asserts that "it must not be forgotten that the MPEP states that if a peptide is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is 'not sufficient for written description purposes, even when accompanied by a method of obtaining the claimed sequence'" and "the number of possible sequences a peptide or protein compounds having pharmaceutical activity is vast." Applicant respectfully submits that the instant claims are drawn to methods of preparing peptides. Because the claimed invention is not particular peptide compositions or sequences having a particular

function, Applicant is unsure of how the Examiner's argument is relevant in the instant case. Applicant respectfully requests clarification.

For all of the reasons discussed above, Applicant respectfully submits that the written description requirement is met for the claimed invention, and Applicant requests that the rejection be removed.

3. **Rejection under 35 U.S.C. § 102(b).** Claims 1-4 and 8 are rejected under under 35 U.S.C. § 102(b) as being anticipated by Bertozzi *et al.* (*Science*, 23 March 2001, 291: 2357-2364). The Examiner finds that the Bertozzi reference teaches "glycoprotein synthesis by convergent coupling of glycopeptide fragments" and that "Bertozzi teaches that one fragment is functionalized as a COOH-terminal thioester, and the other bears an NH_2-terminal cysteine residue." Applicant respectfully submits that the peptide acyl donor of claim 1, which is analogous to the COOH-terminal thioester taught by the Bertozzi reference, is of the formula:



Because the instantly claimed method utilizes a peptide acyl donor comprising a COOH-terminal ester, and not a thioester, the ligation method taught by Bertozzi *et al.* is not within the scope of the claimed invention and therefore cannot anticipate the instant claims. Applicant respectfully requests that the rejection be removed.

4. **Rejection under 35 U.S.C. § 103(a).** Claims 1-4, 8-15, 20, and 22 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hojo *et al.* (*Tetrahedron Letters*, 2003, 44: 2961-2964) in view of Miller *et al.* (*Angew. Chem. Int. Ed.*, Jan. 27, 2003, 42(4): 431-434). Applicant respectfully disagrees. Hojo *et al.* describes the preparation and conjugation of a peptide thioester containing an N-linked core pentasaccharide (see page 2963, right column). Miller *et al.* describes the preparation and conjugation of peptide thioesters. Neither Hojo *et al.* nor Miller *et al.* disclose or teach the activated esters of the present invention. Applicant respectfully

submits that without such a teaching or suggestion, one of ordinary skill in the art would not be motivated to modify the teachings of Hojo *et al.* and Miller *et al.* to arrive at the presently claimed method which uses activated esters, wherein R^{X0} is a disulfide-substituted aryl moiety. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection over Hojo *et al.* and Miller *et al.*

5. **Objection under 35 U.S.C. § 112.** The Examiner states that "the specification is objected to for the following: the specification indicates 'incorporation by reference' of certain documents." The Examiner then quotes from the MPEP, "an application as filed must be complete in itself in order to comply with 35 U.S.C. § 112. Material nevertheless may be incorporated by reference." Applicant is unsure of exactly what the Examiner is objecting to, as the Examiner does not elaborate on which documents incorporated by reference would be deemed "essential material." Applicant respectfully requests clarification.

6. **Miscellaneous Amendments**

Applicant has amended claim 7 to correct typographical errors in the names of the carbohydrate moieties. "STN" has been amended to "STn" and "2,6-STn" has been amended to "2,6-ST". Support for these amendments can be found in Exhibit A, as referenced above, wherein the art-recognized names are designated.

Applicant has amended claim 22 to recite the full name of "MESNa".

Applicant has amended claim 23 to depict the structure of phenylalanine as the amino acid residue directly attached to $-OR^{X0}$. Applicant submits that no new matter is added by the present Amendment.

Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Applicant thanks the Examiner for careful consideration of this case. Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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